Electrophysiological correlates of fearful face recognition in schizophrenia

PhD Theses

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1. INTRODUCTION

The focus of this dissertation, the investigation of the electrophysiological correlates of fearful face recognition impairments in schizophrenia can be best conceived of in the context of social cognition in schizophrenia, an area of research that has come to the attention of cognitive neuroscience research in the past decades. With the shift from positive symptoms as treatment targets to the more devastating negative and cognitive symptoms of the disorder, neuroscience research has adopted the framework of investigating these variables in their association to each other and to functional outcome measures, delineating potential pathways of impairments leading from basic neurocognition, through social cognition and clinical symptoms, to functional outcome. Facial emotion recognition, as a key component of social cognition, can be placed within this framework. Our aim was to investigate the nature of facial emotion recognition impairment in schizophrenia at a neurophysiological level that would possibly render implications for broader levels of information-processing impairments in schizophrenia.

2. OBJECTIVES

General objectives and collaborations

Our research on fearful facial emotion recognition in schizophrenia was embedded in a broader psychophysiological research context with the purpose to gain insight, at the electrophysiological level, into the neural processing of fearful face recognition in schizophrenia and to examine the extent to which this neural processing is disrupted in schizophrenia as compared to healthy controls. To this end our electrophysiology lab team, in collaboration with colleagues from the Psychology Institute at the Hungarian Academy of Sciences, together designed two electrophysiological paradigms to be conducted at the electrophysiology lab at the Department of Psychiatry and Psychotherapy at the Semmelweis University, Budapest, Hungary. My colleagues were Gábor Csukly (Semmelweis University) and Gábor Stefanics (Hungarian Academy of Sciences). Our advisor and mentor was Pál Czobor (Semmelweis University). Professors István Bitter (Semmelweis University) and István Czigler (Hungarian Academy of Sciences) supervised our work.

Experimental paradigms

There were two experimental paradigms designed by our research group to study facial emotion recognition in schizophrenia. The first paradigm was based on a serial visual presentation design, where emotional faces were presented in the focus of visual attention. This paradigm, which probes the processing of attended facial emotional stimuli, constitutes the principal focus of the present dissertation. ERP data acquired using this paradigm were subjected to analyses in two separate investigations: one in the time-domain (**Study 1**) and the other one in the time-frequency domain (**Study 2**).

The second paradigm (**Study 3**) is presented only briefly, as it does not constitute the primary focus of this dissertation but provides subsidiary information in the context of our broader emotion recognition investigation in schizophrenia. With the second paradigm our aim was to investigate the neural processing of unattended emotional facial stimuli in the two groups. To this end, the ERP paradigm applied in this study did not require overt responses to the face stimuli, as facial emotional expressions were presented outside of the attentional focus. This paradigm was based on the extraction of the visual Mismatch Negativity (vMMN) event-related potential.

Specific objectives

STUDY 1: Time-domain characterization of event-related potentials (ERPs) during fearful face recognition in patients with schizophrenia as compared to matched healthy controls

In our first investigation we aimed to evaluate the time sequence and topography in the brain electrical activity through event-related potentials (ERPs) during fearful face recognition in patients with schizophrenia as compared to matched healthy controls. Of particular interest was the temporal and topographical distribution of these electrocortical responses to fearful facial expressions. We also investigated the correlation between electrophysiological measures of fearful facial emotion recognition and emotion recognition performance as measured through the on-line emotion recognition task performed during the EEG recordings. We also aimed to investigate the correlation between bioelectrical changes and symptom dimensions of psychopathology.

STUDY 2: Time-frequency domain characterization of ERPs during fearful face recognition in patients with schizophrenia as compared to matched healthy controls

In our second investigation, using the same data as in the first study, we conducted a time-frequency analysis for both evoked and induced neural activity as captured by the Event Related Spectral Perturbation (ERSP). Event-locked activity was measured by the phase locking factor, the Inter Trial Coherence (ITC). Furthermore, we aimed to investigate the associations between electrophysiological measures of fearful facial emotion recognition and emotion recognition performance as measured through a more detailed off-line emotion recognition task performed after the EEG recordings.

STUDY 3: Visual Mismatch Negativity (vMMN) study of fearful face recognition in schizophrenia

The ERP paradigm applied in this study did not require overt responses to the face stimuli, as facial emotional expressions were presented outside of the attentional focus. This paradigm was based on the extraction of the visual Mismatch Negativity (vMMN) event-related potential. We studied the differences between patients and control subjects by comparing their vMMN responses to unattended rare (deviant) facial emotions embedded in a stream of faces expressing frequent (standard) emotions.

3. METHODS AND MATERIALS

As Study 2 is a second investigation of the same data as in Study 1, and Study 3 was conducted in the same experimental setting as Study 1 and Study 2, the description of *Subjects* is identical in all three studies. *Stimuli*, *Procedures*, *Instruments and measures* and *Recordings* are identical in Study 1 and Study 2, parts beginning with *Data analysis* differ in the first two studies. *Stimuli*, *Procedures* and *Data analysis* of Study 3 will be separately presented.

Subjects

Twenty-four patients meeting the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for schizophrenia (13 men and 11 women, mean age: 34 yr, SD = 10.2) and twenty-four healthy controls (13 men and 11 women, mean age: 33.1 yr, SD = 9.9) were enrolled in the study. Healthy controls were individually matched to the patients by

gender, age (+/- 5 years), and years of education (+/- 3 years), thus resulting in 24 matched pairs. Participants did not receive payment for their participation, and provided written informed consent after all procedures were fully explained according to procedures approved by the Institutional Review Board of the Semmelweis University, Budapest, Hungary. Patients were recruited from both the inpatient and outpatient units of the Department of Psychiatry and Psychotherapy of the Semmelweis University, Budapest (inpatient: outpatient ratio = 9:15). All patients were assessed on the Positive and Negative Syndrome Scale (PANSS) by a trained psychiatrist or psychologist. All patients were taking antipsychotic medication at the time of testing (mean chlorpromazine equivalent dose of 601 mg/day, SD=445.5). The ratio of schizophrenia subtypes among patients was as follows: 13 paranoid, 2 catatonic, 6 disorganized, and 3 undifferentiated.

Stimuli (Study 1 and Study 2)

The facial stimuli used in the experiment were chosen from Ekman and Friesen's Face stimuli with hair removed from the stimuli to avoid gender cues other than facial structure and features. After standardizing the size, resolution and luminance, the photographs were cropped to produce an ellipse-shaped image that contained only the face with the eyebrows, eyes, nose, and mouth of the individual on a dark grey background. Five female and five male faces were used, each displaying a neutral and a fearful expression, yielding altogether 20 stimuli.

Procedures

The experiment lasted approximately 2.5-3 hours, including initial screening, EEG recordings and tests. Participants were first informed about the study, procedures, and a written informed consent was obtained by them. Then a general screening test, the SCL-90 was administered for each participant. Participants were applied a 128-channel electrode cap. The experiment was programmed and presented with the Presentation 13.0 software (Neurobehavioral Systems, Inc.). Stimuli were presented for 200ms, followed by a blank screen with a fixation cross until the participant’s behavioural response. The interval between the response and presentation of subsequent stimulus varied between 600ms and 700ms. As non-face control stimuli, phase-randomized patches were generated from the Ekman-faces that contained all of the same visual information as the face stimuli used, just “scrambled” up. Stimuli (faces) were phase-randomized using the ’Weighted mean phase (WMP) type phase scrambling'. These

patches were presented at a 1:4 ratio to facial stimuli, also for 200ms. Occasionally (at a 1:10 ratio to stimuli) a schematic picture of an eye was presented to the participants for 1000ms followed by a 1000ms interval of a blank screen, giving them the chance to blink and thus to achieve reduction in blink-related artefacts during facial stimulus presentation.

Participants were instructed to respond as quickly and accurately as possible by pressing one of two buttons whenever they perceived the facial expression displayed as neutral, and the other button whenever they perceived the facial expression displayed as fearful. No response was asked to be given to the non-face patches and to the schematic eye.

Instruments and measures

PANSS – Positive and Negative Symptom Scale (Kay et al., 1987)

The scale has seven positive-symptom items, seven negative-symptom items and 16 general psychopathology symptom items. Each item is scored on a seven-point severity scale. The 30-item PANSS was conceived as an operationalized instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology.

SCL-90 – Symptom Checklist – 90 (Derogatis LR, 1977)

The Symptom Checklist-90 (SCL-90) is a general screening measure used as a method for screening and detecting clinical symptoms or indicators of psychological distress. It is one of the most widely used measures of multiple aspects of psychological distress in clinical practice and research. SCL-90 includes 90 item rated on 5-point scale, ranging from 0= not at all, to 4= extremely. SCL-90 measures nine primary distress dimensions: somatization; obsessive compulsive; interpersonal sensitivity; depression; anxiety; hostility; phobic anxiety; paranoid ideation; and psychoticism. According to the Derogatis criteria for ‘caseness' (i.e.: high risk for a psychiatric disorder), a global severity index of >114 on the SCL-90 was an additional exclusion criteria for healthy controls (DeRogatis and Melisaratos, 1983; Unoka, 2004). The Hungarian version of the SCL-90 was validated by Unoka et al (2004). No subjects were excluded from the control group based on these criteria.

Ekman-60 faces test

This computer-based test is one of the components of the Facial Expressions of Emotion—Stimuli and Tests (FEEST; Young, 2002). Sixty facial expressions were presented in a

random order on a computer screen and participants indicated, using the mouse to click on the appropriate button at the bottom of the screen whether the emotion expressed was happiness, sadness, anger, fear, disgust or surprise. Each image remained on the screen for a maximum of five seconds; presentation of the next image was triggered by the participant responding to the previous one, to avoid time pressure.

Recordings

EEG was recorded from DC with a low-pass filter at 100 Hz using a high-density 128-channel BioSemi ActiveTwo amplifier. The electrode cap covered the whole head with an equidistant-layout. Eye movements were monitored by two electrooculogram (EOG) electrodes placed below the left and above the right external canthi. Data were digitized at 24 bit resolution and a sampling rate of 512 Hz. Subsequent data analyses were carried out off-line using built-in and self-developed functions as well as the EEGLAB Toolbox in Matlab. Further statistical analyses were carried out using the SAS ® 9.2 software. EEG was re-referenced to the common average potential and filtered off-line between 0.1 and 30 Hz using zero-phase shift Butterworth filter. Epochs of 100ms prestimulus to 600ms poststimulus were extracted from the continuous EEG for further analysis and corrected for prestimulus baseline. To avoid potential artifacts, epochs with a voltage exceeding ±120 μV on any EEG or EOG channel were rejected from the analysis.

Data analysis (Study 1)

As a preliminary analysis and "quality check", we investigated whether a face-specific response (N170 component) was detectable in our neutral facial stimuli as compared to the non-face patches. To this end, we used the General Linear Model (GLM) analysis.
In our principal analyses, first we aimed to identify the time periods during which any of the two groups showed a statistically significant discrimination in the ERPs for the fearful vs. neutral stimuli. Second, we aimed to test whether in the identified time periods there was a significant difference between the ERP waveforms between the two groups. Finally, we aimed to delineate the group differences in the scalp topography of ERPs that are associated with facial emotion processing.

In particular, affect-related modulations for each of the ERP time intervals were tested by computing the difference wave for the fear vs. the neutral stimuli using the Global Field

Power (GFP). Random Regression Hierarchical Linear Modeling (HLM) was the primary statistical approach. Analogous HLM analyses were conducted for the reaction time and error data, as well as for the ERP amplitudes in exploratory analyses in each of 5 brain regions of interest: frontal, central, parietal, temporal, and occipital areas.

GFP difference waveforms were determined separately in the two study groups by subtracting the GFP to fearful stimuli from the GFP to neutral stimuli. Then we analyzed the GFP difference waveforms in order to identify emotion effects, i.e., to identify the time intervals where they significantly differed from zero (i.e., an effect of emotion on the ERPs was detectable). Based on this approach the time windows in the mid-latency (150-170ms) and late latency (330-450ms) range were selected for further analysis.

In further exploratory analyses we investigated the topographical specificity of the group differences in the later (330-450ms) latency range. In order to reduce the spatial dimensions of the data set, we conducted analyses for 5 clusters of electrodes corresponding to conventional topographical regions (frontal, central, parietal, temporal, and occipital areas).

Association between potentially important covariates, such as behavioral indices, clinical symptoms of schizophrenia, and medication as a confounder with the GFP difference values were investigated by HLM analyses.

Data analysis (Study 2)

In our time-frequency approach, stimulus-related theta activity changes were measured by calculating the event-related spectral perturbation (ERSP), which is a 2-D image of mean change in spectral power (in dB) from baseline. The ERSP measures average dynamic changes in amplitude of the broad band EEG frequency spectrum as a function of time relative to an experimental event. Stimulus-locked evoked activity was measured by inter-trial coherence (ITC), which is the 2-D image of strength (0 to 1) of the phase-locking of the EEG signals to the time-locking events.

Based on our previous results, the 140-200ms time window (+/- 30ms around 170ms) was selected for analysis.

The different effects on ERSP and ITC were tested by three-way analyses of covariance (ANCOVA). The associations of emotion recognition performance (as indexed by the FEEST) with ERSP and ITC were investigated by Pearson correlation. Relationship between ERSP, ITC and emotion recognition performance during EEG was examined by Spearman correlation in both study groups separately.

Stimuli and procedure (Study 3)

Stimulus presentation was designed in a manner to facilitate the forming of memory traces to emotions rather than to individual faces. To this end, black and white photographs of 5 female and 5 male faces were used as stimuli, taken from the Pictures of Facial Affect set, as in Studies 1 and 2. On each screen, 4 images of faces expressing the same emotion, specifically, images of 2 males and 2 females expressing the same facial emotion (happy or fearful) were presented in the upper-left, upper-right, lower-left and lower-right quadrants of the monitor. Faces presented outside the center of the visual field enable studying mismatch responses to deviants without attentional confounds. In the center of the monitor a black fixation cross was presented. Pictures appeared on a dark-grey background at a viewing distance of 0.5 m. The presentation order of the individual pictures was randomized with the restriction that a picture of the same person was not presented on subsequent stimulus displays. Stimulus duration was 200ms. In two experimental blocks fearful facial emotions were presented as frequent standards and happy facial emotions were presented as rare deviants (standard P=0.9, deviant P=0.1). In the remaining two blocks the standard and deviant emotions were swapped. The order of the four blocks was randomized across participants. A total of 100 deviant and 900 standard stimuli were presented for each emotion. The task of the subjects was a feature detection task entirely unrelated to the change in the facial expressions, with the purpose to "distract" their attention from the faces: they had to respond with a speeded button-press to the unpredictable changes in the length of either the horizontal or vertical lines of a black fixation cross presented in the center of the visual field. From time to time, the cross became either wider or longer, with a mean frequency of 11 changes per minute (SD=3).

Data Analysis (Study 3)

Difference waveforms (mismatch responses) were created by subtracting ERPs to standards from the ERPs to deviants, separately for the two emotions. In half of the blocks the roles of deviants and standards were reversed, responses to standard fearful faces were subtracted from responses to deviant fearful faces, and responses to standard happy faces were subtracted from responses to deviant happy faces. Six Regions of Interest (ROIs) were formed: pre-frontal, central, temporal left, temporal right, occipital left and occipital right. Mean ERP responses were calculated by averaging across electrodes within ROIs. Time windows of 170-220ms and 250-360ms were selected for analyses based on results from the

same control population. Difference between study groups was investigated by ANOVA with mismatch response amplitude as dependent and study group as independent variable.

4. SUMMARY OF RESULTS (STUDIES 1-3)

We have shown that patients significantly differ from healthy controls in several aspects of electrophysiological and behavioral measures, and that differential responses are obtained via these indices as a function of face vs non-face stimuli and as a function of fearful vs neutral face stimuli. Our summary of main findings are the following:

1) We found evidence for differential processing of fearful vs. neutral faces between schizophrenia patients and healthy controls in terms of evoked brain responses, as indexed by the GFP. This was manifested in the later stages (330-450ms) of emotion processing.
2) In schizophrenia subjects, differentiation between fearful vs neutral faces was modulated by clinical symptomatology of fear: positive symptoms seemed to enhance neural hyperresponsivity to fear, while negative symptoms seemed to attenuate the neural response to fear.
3) A posteriorization and hypofrontality effect in the patient group was shown by differential ERP response topography to fearful vs. neutral faces among patients compared to healthy controls, which was reflected in a pronounced activation mostly in the occipital regions and absence of activation in the frontal regions.
4) Event-related changes in theta oscillatory activity as indexed by the ERSP and inter-trial phase coherence (ITC) were significantly weaker in patients with schizophrenia as compared to healthy controls in the time interval of 140-200ms post-stimulus.
5) Event-related changes in theta oscillatory activity as indexed by the ERSP and inter-trial phase coherence (ITC) to facial expressions but not to non-face stimuli predicted emotion recognition performance in both groups in the time interval of 140-200ms post-stimulus.
6) While there was no overt behavioral differentiation in an online emotion recognition task between fearful vs. neutral faces in either of the study groups, control subjects significantly outperformed patients on the offline emotion recognition task as indexed by the FEEST.

7) Visual mismatch (vMMN) responses were reduced in schizophrenia patients as compared to healthy controls in both the 170-220ms and 250-360ms time windows and vMMN responses correlated with emotion recognition performance.

5. CONCLUSIONS

To our knowledge, our studies are among the first in the schizophrenia literature to examine both time-domain and time-frequency decomposition of EEG in matched groups of schizophrenia patients and healthy controls in response to fearful facial stimuli using a high density EEG electrode array. Our findings show not only deficits in both ERPs and theta oscillatory activity during the processing of fearful faces in schizophrenia, but we also found correlations in both groups between the EEG measures in response to faces and behavioral performance on a facial affect recognition task.

Regarding face-specific information processing, our results of both ERPs and theta oscillatory activity corroborate the established finding that the 140-200ms time window reflects a face-specific processing stage that might be selectively sensitive in the structural decoding of faces. Our results also confirm the finding that theta activity in this time window plays a prominent role in face-specific information processing, as in both groups electrocortical activity proved to be sensitive only to facial stimuli as compared to non-faces in this time window. Also our correlational results between EEG indices and behavioral indices in this time window underline the presence of a face-specific processing stage.

Specifically, the fact that theta oscillatory activity was significantly reduced in the schizophrenia group as compared to healthy controls in the face-specific time window corroborates a structural decoding deficit in schizophrenia, which could be demonstrated for fearful faces in our experiments.

A deficit in the processing of emotional content of fearful faces in the schizophrenia group in our study was suggested by a hyperreactivity in a later, 330-450ms time window, this neural reactivity being absent in healthy controls. Furthermore, the topographical pattern of a relative hypofrontal – hyperposterior activation to fearful faces in the schizophrenia group as seen in our results might indicate less effective facial emotion decoding routes in the patient group. Also, our supplementary results of Study 3 demonstrate that impairment of facial emotion processing in schizophrenia is present already at the automatic, unconscious level.

In sum, our results suggest a deficit affecting both the structural and emotional decoding of fearful faces in schizophrenia patients during fearful facial emotion processing. The underinvolvement of inhibitory cortical mechanisms to emotionally salient stimuli, and the use of alternative processing mechanisms might be an approach to further pursue and explain affective and cognitive deficits in facial emotion recognition in schizophrenia. Our findings thus lend support to the notion that cortical markers of facial discrimination could be validly considered as vulnerability markers in schizophrenia.

6. LIST OF PUBLICATIONS

Publications related to the dissertation

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